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Effect of Corneal Cross-linking versus Standard Care on Keratoconus Progression in Young Patients

The KERALINK Randomized Controlled Trial

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Purpose: To examine the efficacy and safety of corneal cross-linking (CXL) for stabilization of progressive keratoconus.

Design: Observer-masked, randomized, controlled, parallel-group superiority trial.

Participants: Sixty participants 10 to 16 years of age with progressive keratoconus, one eye of each deemed the study eye.

Methods: The study eye was randomized to either CXL plus standard care or standard care alone, with spectacle or contact lens correction as necessary for vision.

Main Outcome Measures: The primary outcome was steep keratometry (K2) in the study eye as a measure of the steepness of the cornea at 18 months. Secondary outcomes included keratoconus progression defined as a 1.5-diopter (D) increase in K2, visual acuity, keratoconus apex corneal thickness, and quality of life.

Results: Of 60 participants, 30 were randomized to CXL and standard care groups. Of these, 30 patients in the CXL group and 28 patients in the standard care group were analyzed. Mean K2 in the study eye 18 months after randomization was 49.7 D (standard deviation [SD], 3.8 D) in the CXL group and 53.4 D (SD, 5.8 D) in the standard care group. The adjusted mean difference in K2 in the study eye was −3.0 D (95% confidence interval [CI], −4.9 to −1.1 D; $P = 0.002$), favoring CXL. Adjusted differences between groups in uncorrected and corrected vision favored eyes receiving CXL: −0.31 logarithm of the minimum angle of resolution (logMAR; 95% CI, −0.50 to −0.11 logMAR; $P = 0.002$) and −0.51 logMAR (95% CI, −1.37 to 0.35 logMAR; $P = 0.002$). Keratoconus progression in the study eye occurred in 2 patients (7%) randomized to CXL compared with 12 patients (43%) randomized to standard care. The unadjusted odds ratio suggests that on average, patients in the CXL arm had 90% (odds ratio, 0.1; 95% CI, 0.02−0.48; $P = 0.004$) lower odds of experiencing progression compared with those receiving standard care.

Conclusions: CXL arrests progression of keratoconus in the majority of young patients. CXL should be considered as a first-line treatment in progressive disease. If the arrest of keratoconus progression induced by CXL is sustained in longer follow-up, particular benefit may be derived from avoiding a later requirement for contact lens wear or corneal transplantation. *Ophthalmology 2021;■:1−11 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Keratoconus, characterized by distortion and thinning of the cornea, is usually bilateral, but can be asymmetric. In its early stages, keratoconus causes worsening of vision resulting from increasing myopia and irregular astigmatism. Spectacle correction can provide good visual acuity only in early disease, until increasingly irregular astigmatism requires correction with rigid contact lenses for best vision. If lenses are not tolerated, these individuals can be functionally blind in affected eyes. Patients with more advanced keratoconus lose contact lens–corrected visual acuity as a result of corneal opacification and require corneal replacement by transplantation. Reported keratoconus prevalence is 1:375 (265 per 100 000) in The Netherlands,[1] 1:84 in Australian 20-year-olds,[2] and as high as 1:45 in some ethnic groups.[3] Onset is rare before the age of 10 years, and the age at diagnosis is usually between 15 and 30 years, with progression in affected eyes until spontaneous stabilization in the mid thirties. Diagnosis

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and monitoring of progression is by corneal tomography, which quantifies irregularity of corneal curvature and corneal thickness.

Although standard care involves treatment of the refractive consequences of keratoconus or replacement of the diseased cornea by a transplant, the concept of arresting progression of keratoconus at an early stage when good unaided or spectacle-corrected vision remains is relatively recent. Corneal cross-linking has been reported to be effective in arresting keratoconus progression in most treated adult eyes based on evidence from 3 randomized controlled trials,[4–6] but the findings are limited by uncertainty (wide confidence intervals [CIs]) and likely risk of bias.[7] Cross-linking increases the biomechanical rigidity of the cornea, but direct ultrastructural evidence of the mechanism of action has not been found.[8]

Keratoconus often is more advanced if first diagnosed in children than in adults, and some suggest faster subsequent disease progression.[9–11] A number of retrospective observational studies of cross-linking in younger patients, with varying age ranges and durations of follow-up, have reported a beneficial effect of cross-linking.[12–17] Treatment of young patients by conventional (Dresden) and accelerated cross-linking protocols have been reported to be similarly effective.[18] However, more robust randomized evidence is required to inform practice, particularly in children and adolescents, about whom few studies have been published. Given that subclinical or early keratoconus can be detected by tomography in young patients and that cross-linking may be able to halt disease progression, an opportunity exists to stabilize disease at an early stage, before the requirement for contact lenses or corneal transplantation. The KERALINK randomized controlled trial assesses the efficacy and safety of cross-linking in 10- to 16-year-olds with progressive keratoconus to determine whether cross-linking plus standard care stabilizes progressive keratoconus, is associated with better vision and quality of life (QoL), and is safe compared with standard care alone.

Methods

Study Design and Participants

The KERALINK trial is an observer-masked, individually randomized, controlled, parallel-group superiority trial. The trial protocol is published[19] and available online: https://www.journalslibrary.nihr.ac.uk/programmes/eme/142318/#/.

The KERALINK trial was approved by the UK Health Research Authority, the Medicines and Healthcare Products Regulatory Agency, and ethics approval was granted by the Brent Ethics Committee (identifier, 16/LO/0913). The trial adhered to the tenets of the Declaration of Helsinki. Consecutive newly referred patients at 4 United Kingdom hospitals 10 to 16 years of age with suspected keratoconus were identified. Keratoconus was confirmed in one or both eyes by corneal tomography (Pentacam HR; Oculus GmbH), and patients were monitored every 3 month for progression. To differentiate true keratoconus progression from measurement artefact, an increase over an interval of at least 3 months in the mean corneal power in the steepest meridian (K2) or maximum keratometry in the steepest corneal power (Kmax) of at least 1.5 D in one or both eyes was used as the threshold for eligibility.[20] For each patient, the eye with the more advanced keratoconus at baseline was categorized as the study eye, unless that eye had undergone prior surgery such as corneal transplantation. Patients with corneal apex thickness of less than 400 μm were excluded (therefore, all study eyes had keratoconus classified as Amsler-Krumreich stage I and II[21]). Additional exclusion criteria were corneal opacification, corneal apex thickness of less than 400 μm, K2 of more than 62 D, Down syndrome, or inability to abstain from contact lens wear for 7 days before follow-up tomography examinations. Written informed consent was obtained from parents of all recruited participants. This trial is registered in the European Union clinical trials register (EudraCT identifier, 2016-001460-11).

Baseline Assessment

At baseline all patients were assessed as set out in Table 1.

Randomization and Masking

Randomization used a minimization algorithm incorporating a random element with minimization factors of treatment center and whether progression was confirmed in one or both eyes at randomization. After verification of eligibility, a web-based randomization service (https://www.sealedenvelope.com) issued a randomization assignment. Participants were randomized in a 1:1 ratio to either cross-linking or standard care in the study eye. Because of the invasive nature of the cross-linking intervention, neither the trial participants nor the treating clinicians were masked to the treatment allocation. However, optometrists performing all outcome examinations and questionnaire evaluations were masked as to the randomized allocation. The treating clinicians were masked to primary outcome data (K2) measured by optometrists during the follow-up assessments.

Cross-linking Procedure

Cross-linking was performed under local or general anaesthesia in one or both eyes (according to whether progression was confirmed in one eye or both). After removal of the corneal epithelium with a spatula and administration of riboflavin drops (Vibex Rapid; Avedro) every 2 minutes for 10 minutes, ultraviolet light was applied using standardized parameters of 10 mW/cm^2 for a 5.4-J/cm^2 total energy dose administered over 9 minutes in a continuous manner (Avedro KXL).[19] At completion of the procedure, a protective contact lens was applied to the eye until corneal epithelialization was complete. Subsequent management with topical steroid and topical antibacterial prophylaxis is described elsewhere.[19] Participants randomized to cross-linking received spectacle or contact lens correction as necessary for the study eye, as in the standard care comparator trial arm.

Standard Care

The trial control arm was standard management alone, including refraction testing with provision of glasses or contact lens fitting, or both, for one or both eyes as required for best-corrected visual acuity. Participants randomized to standard care with confirmed progression (see below) were offered cross-over to the cross-linking arm; this was undertaken no earlier than 9 months after randomization.[19]

Outcomes

The most important parameters used in the assessment of progression of keratoconus are the curvature of the cornea (measured as diopter power, designated K), corneal thickness in micrometers,

Table 1. Baseline Assessments of the Study Eye and Quality of Life

Type of Assessment	Findings
Corneal tomography	Measurement of corneal power in steepest meridian (K2) and maximum power (Kmax), triplicate*
Visual acuity	Unaided or with preferred correction (logMAR)
Refraction	Subjective, both eyes
Apical corneal thickness measurement	Ultrasonic pachymetry† and Pentacam imaging
Quality of life	Vision related (CVAQC),[17] generic pediatric health outcome (CHU9D)[18]

CHU9D = Child Health Utility 9D; CVAQC = Cardiff Visual Ability Questionnaire for Children.
*Mean of triplicate measurements were used in assessment of progression for eligibility, baseline, and all follow-up assessments.
†Pachmate DGH55 (DGH Technology, Inc, Exton, PA).

refraction, and best-corrected visual acuity. The primary outcome measure was mean corneal power in the steepest meridian (K2) in the study eye, measured using corneal tomography at 18 months after randomization. The mean of triplicate K2 measurements at baseline and at each follow-up assessment were used in the analyses. Secondary outcomes were keratoconus progression, defined as a K2 increase of more than 1.5 D, unaided and best-corrected visual acuity, corneal thickness at the keratoconus apex, and vision-related QoL assessed by the 25-item Cardiff Visual Ability Questionnaire for Children[22] and Child Health Utility 9D[23] questionnaires. Safety was documented in all participants.

Statistical Analysis

All study analyses were carried out according to a predefined statistical analysis plan, reported elsewhere.[24] On the basis of a previous study of cross-linking in adults,[6] we estimated that a sample size of 60 patients would be required to detect a difference between the 2 groups of 1.5-D in the change in K2 at 18 months after randomization. These calculations were based on a common standard deviation (SD) of 1.5 D, 90% power, and a type 1 error rate of 5%. Additionally, we allowed for a loss to follow-up rate of 24%. All efficacy analyses were conducted following the intention-to-treat principle, where all randomized patients were analyzed in their allocated group regardless of whether they received their randomized treatment. If a tomography scan was categorized as being of unreliable quality by a red flag indicator on the Pentacam software, then the K2 measurement from that scan was not used. For the primary analysis, the mean K2 at each visit was calculated using measurements from reliable scans only. Two patients were considered to have missing K2 data at the 18-month visit because all 3 scans had an associated red flag indicator (Fig 1). We did not perform multiple imputation because minimal data were missing.

A multilevel repeated measures linear regression model was used to estimate the difference between the treatment groups in K2 values at 18 months. The model included fixed effects for K2 at randomization, treatment group, time, treatment by time interaction, and the minimization factors center and number of eyes progressed at randomization. A random patient effect was included to take account of clustering within patients. The model coefficients were estimated using the robust standard errors technique to allow for unequal variances in the 2 randomized groups. Model assumptions were assessed using residual plots. We carried out prespecified subgroup analysis by whether a history of atopy was reported and by ethnicity. All statistical tests used a 2-sided P value of 0.05, unless otherwise specified. No formal adjustments of P values were made according to our statistical analysis plan. Two-sided 95% CIs were presented for all estimates. Findings for the secondary outcomes are not corrected for multiple comparisons.[25] The CIs and statistical tests are considered to provide supportive evidence in relationship to the primary objective and additional clinical characterization of treatment effects. STATA/MP software version 15.0 (Stata Corp) was used for all analyses.

Results

Between October 28, 2016, and September 26, 2018, 240 patients were screened for eligibility, 60 of whom were assigned randomly to either cross-linking or standard care in the study eye. The number of participants recruited and included in the analysis is set out in Figure 1. Two patients receiving standard care withdrew from the trial before the 3-month follow-up visit. A further 2 patients were lost to follow-up or discontinued the study after the 3-month visit, but their data were included in the intention-to-treat analysis. One patient in the cross-linking group did not undergo the randomized procedure, having withdrawn consent, but continued follow-up assessments as per protocol.

Baseline demographic and ocular characteristics are shown in Table 2. Patients randomized to cross-linking included a higher proportion of male participants (83% vs. 63%) and a higher proportion of White people (40% vs. 17%) compared with those in the standard care group. Mean age of the participants was similar in both treatment arms: 15 years (SD, 1.1 years) in the cross-linking arm and 15 years (SD, 1.6 years) in the standard care arm. Overall, 45% were of South Asian or Asian British ethnicity. Seven patients (12%) showed progression in both eyes meeting the eligibility criteria for randomization. For these patients, the eye with the most advanced disease was deemed to be the study eye and received randomized treatment. Sixty-eight percent of patients were using a refractive corrective aid at baseline; most (85%) used glasses, 5 patients used both glasses and contact lenses, and 1 patient reported using only contact lenses. Of those using contact lenses, 3 patients reported using rigid contact lenses at baseline. Mean K2 in the study eye was 49 D (SD, 3.5 D) in patients randomized to cross-linking and 50 D (SD, 3.4 D) in patients randomized to standard care. The baseline measurements, including uncorrected visual acuity, best-corrected visual acuity, apical corneal thickness, and Kmax for the study eye, are summarized in Table 2. The table also includes baseline QoL scores of patients measured using the 25-item Cardiff Visual Ability Questionnaire for Children and Child Health Utility 9D questionnaires.

Findings for the primary outcome, K2 in the study eye, are set out in Figure 2 and Table 3. At 18 months, cross-linking patients showed a mean K2 of 49.7 D (SD, 3.8 D) compared with 53.4 D (SD, 5.8 D) in standard care patients. The adjusted difference of −3.0 D (95% CI, −4.93 to −1.08 D) suggests that on average, patients who received cross-linking in the study eye had a K2 that was 3 D lower than those in the standard care arm at 18 months after randomization. This difference is statistically significant (P = 0.002). The 95% CI contains the clinically important difference of

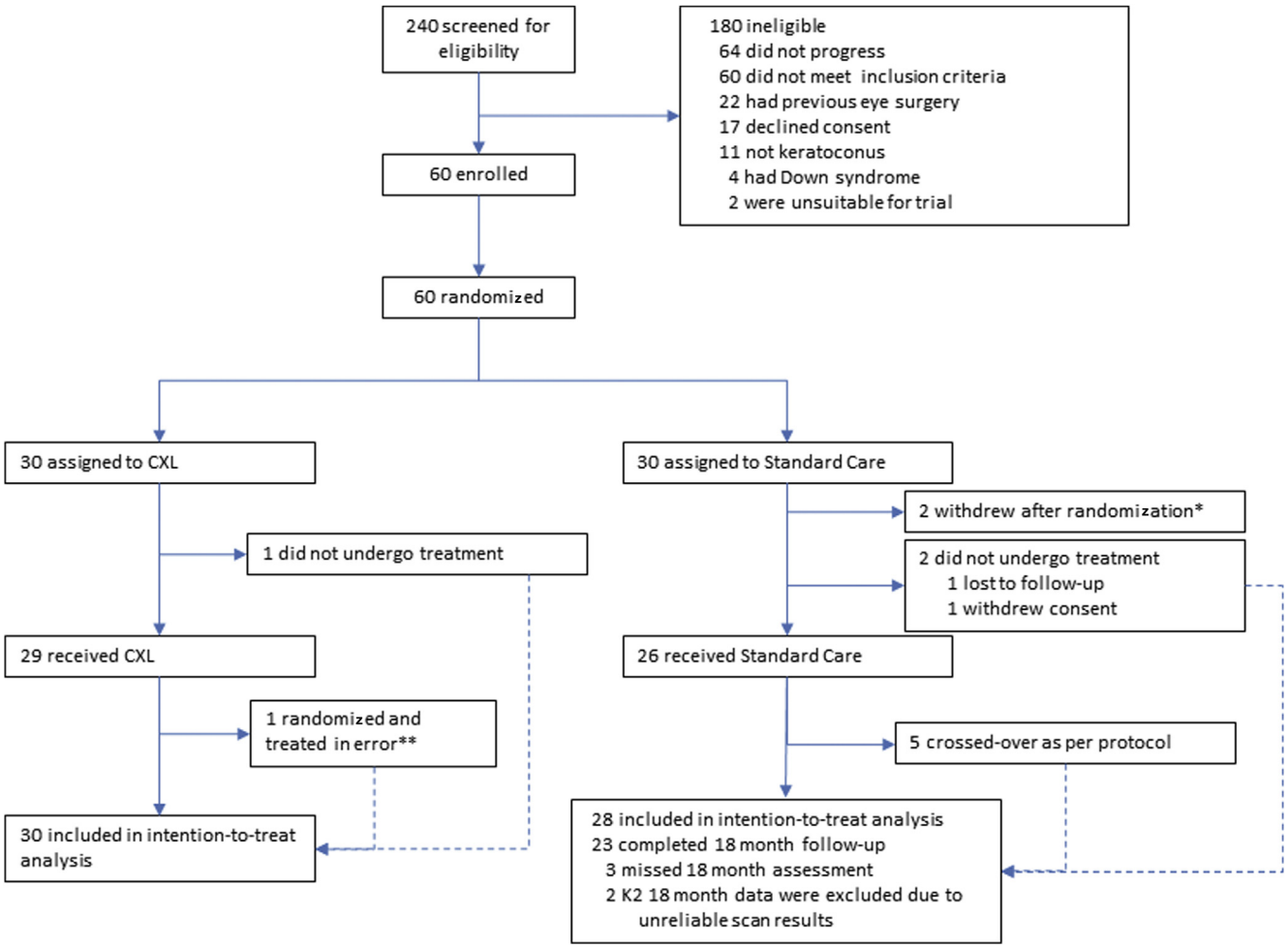

Figure 1. Consolidated Standards of Reporting Trials diagram showing study profile. All 58 patients who underwent baseline keratometry in the steepest meridian (K2) measurement and at least 1 follow-up were included in the mixed model for the primary outcome analysis. *Two participants who withdrew before the 3-month follow-up examination could not contribute data to the primary outcome but were included in the baseline characteristics table. **One further patient randomized to cross-linking (CXL) subsequently was found to have prerandomization K2 increase of 1.2 D and therefore did not meet the 1.5-D K2 increase criterion for trial eligibility. Because the patient already had undergone cross-linking in the study eye when this error was discovered, we continued to follow up the patient; a protocol deviation was recorded.

1.5 D, which corresponds to keratoconus progression. Five patients crossed over from standard care to cross-linking between 12 and 18 months (as per protocol provision), and 1 patient in the cross-linking arm did not undergo their allocated procedure. A further patient randomized to cross-linking subsequently was found to be ineligible for the trial. Because the patient already had undergone cross-linking when this error was discovered, follow-up continued. Per-protocol analysis excluding this patient at baseline, and patients at the time of cross-over did not change the observed intention-to-treat results. Data from patients were excluded at some visits from the mean K2 calculation because of tomography measurements categorized as unreliable by Pentacam software (designated by a red flag). It is recognized that repeatability of tomography scans is reduced in eyes with advanced keratoconus.[20,26] To evaluate the impact of inclusion of these patients with advanced disease on the observed treatment difference, we carried out exploratory sensitivity analysis on the primary outcome by including K2 measurements from red-flagged scans of patients with advanced disease (Supplemental Material and Fig S1, available at www.aaojournal.org). The difference in means between the treatment arms increased at 18 months in Figure S1 compared with that in Figure 2.

Findings for the secondary outcomes are set out in Table 4. Increasing difference was found in mean uncorrected and best-corrected visual acuity between the groups at follow-up visits (Fig 3A, B). Adjusted analysis shows that, on average, patients in the cross-linking group showed significantly lower logMAR values for uncorrected and best-corrected visual acuity compared with those receiving standard care ($P = 0.002$ and $P = 0.002$, respectively; Table 4), indicating that patients randomized to cross-linking achieved significantly better visual acuity at 18 months. We found no significant differences at 18 months between the cross-linking and standard care groups in apical corneal thickness (Fig 3C) and refraction measured as spherical equivalent. Mean Kmax in the study eye at 18 months after randomization was 57 D (SD, 6.2 D) in the cross-linking arm and 60 D (SD, 7.7 D) in the standard care arm. The adjusted difference in Kmax of −2.11 D (95% CI, −4.81 to 0.60 D) at 18 months was not statistically significant ($P = 0.13$). No significant differences were found in patients' quality of life at 18 months as measured using the 25-item Cardiff Visual Ability

Table 2. Baseline Demographic and Ocular Characteristics of the Intention-to-Treat Population

	Cross-linking (n = 30)	Standard Care (n = 30)	Total (n = 60)
Minimization factors			
Treatment center			
Moorfields	25 (84)	25 (84)	50 (83)
Sheffield	2 (7)	4 (13)	6 (10)
Liverpool	1 (3)	0 (0)	1 (2)
Royal Gwent	1 (3)	0 (0)	1 (2)
Manchester	1 (3)	1 (3)	2 (3)
No. of eyes with progression			
1	27 (90)	26 (87)	53 (88)
2	3 (10)	4 (13)	7 (12)
Patient characteristics			
Age (yrs)	15.2 ± 1.1	15.2 ± 1.6	15.2 ± 1.4
Gender			
Male	25 (83)	19 (63)	44 (73)
Female	5 (17)	11 (37)	16 (27)
Ethnicity			
White	12 (40)	5 (17)	17 (28)
Mixed	4 (13)	2 (7)	6 (10)
Asian or Asian British	10 (34)	17 (56)	27 (45)
Black or Black British	3 (10)	4 (13)	7 (12)
Other ethnic groups	1 (3)	2 (7)	3 (5)
Use of refractive correction aid			
No	9 (30)	10 (33)	19 (32)
Yes	21 (70)	20 (67)	41 (68)
Refractive correction aid			
Glasses	18 (60)	17 (57)	35 (58)
Contact lenses	0 (0)	1 (3)	1 (2)
Both	3 (10)	2 (7)	5 (8)
Type of lenses			
Soft lenses	3 (10)	0 (0)	3 (5)
Rigid gas permeable	0 (0)	3 (10)	3 (5)
Family history of keratoconus			
No	24 (80)	28 (93)	52 (87)
Yes	6 (20)	2 (7)	8 (13)
History of atopy			
No	20 (67)	14 (47)	34 (57)
Yes	10 (33)	16 (53)	26 (43)
Study eye characteristics			
K2 (D)	49.1 ± 3.5	50.2 ± 3.4	49.7 ± 3.5
Kmax (D)	56.0 ± 4.8	57.2 ± 5.7	56.6 ± 5.3
Uncorrected visual acuity (logMAR)	0.6 ± 0.4	0.7 ± 0.4	0.7 ± 0.4
Best-corrected visual acuity (logMAR)	0.5 ± 0.4	0.5 ± 0.4	0.5 ± 0.4
Apical corneal thickness (μm)	512 ± 47.9	507 ± 41.2	509 ± 44.5
Refraction (spherical equivalent) (D)	−0.6 ± 2.3	−1.0 ± 1.6	−0.8 ± 2.0
CVAQC score	−1.1 ± 1.0	−1.2 ± 1.1	−1.2 ± 1.0
CHU9D utility score	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1

CHU9D = Child Health Utility 9D; CVAQC = Cardiff Visual Ability Questionnaire for Children; D = diopter; Kmax = maximum keratometry in the steepest meridian; K2 = keratometry in the steepest meridian; logMAR = logarithm of the minimum angle of resolution.
Data are presented as mean ± standard deviation or no. (%).

Questionnaire for Children and Child Health Utility 9D questionnaires. By 18 months, 2 patients (7%) in the cross-linking arm had experienced keratoconus progression, compared with 12 patients (43%) receiving standard care. The unadjusted odds ratio suggests that, on average, patients in the cross-linking arm have 90% (odds ratio, 0.1; 95% CI, 0.02 to 0.48; $P = 0.004$) lower odds of experiencing progression compared with those receiving standard care. Cox proportional hazards regression of time to progression suggests an 87% lower hazard for the cross-linking arm. Figure 4 shows the Kaplan-Meier plot of time to progression in the 2 arms. There were no serious adverse events reported during the trial.

No significant interaction was found between treatment allocation and a history of atopy ($P = 0.59$) or ethnicity ($P = 0.95$). We also carried out a post hoc comparison of those patients in whom progression occurred and those in whom it did not by age and ethnicity. We were unable to demonstrate a difference in average age between the groups ($P = 0.31$) and we found no significant association between progression and ethnicity ($P = 0.21$). Because these were not prespecified analyses and in particular because the age of recruited patients was skewed toward the upper end of the range, this test may not be sufficiently sensitive to detect such an effect.

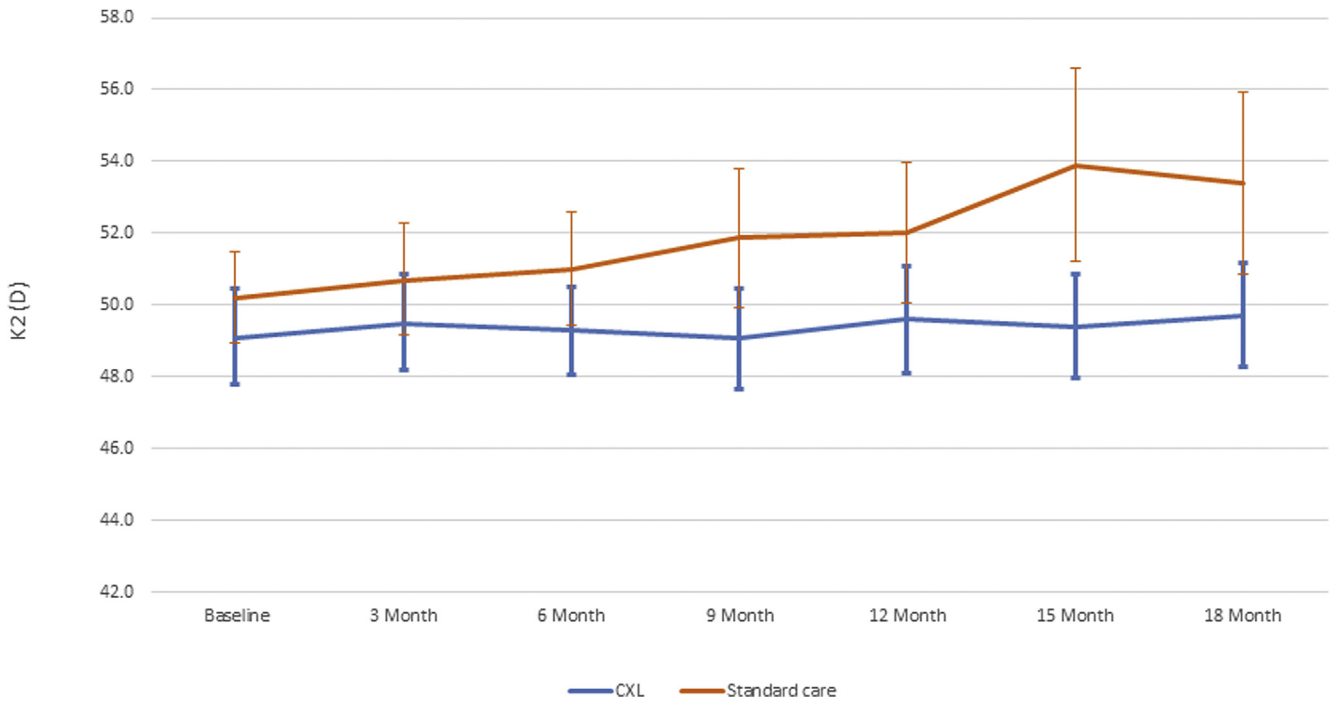

Figure 2. Line graph showing mean corneal power in the steepest meridian (K2) values, measured in diopters (D), in the study eye in patients in the corneal cross-linking (CXL) and standard care groups in primary outcome population at study visit intervals. Data are means. Error bars represent 95% confidence intervals of the mean.

Discussion

In this observer-masked randomized controlled trial involving young patients 10 to 16 years of age, we found that at 18 months, participants randomized to cross-linking plus standard care were less likely to demonstrate clinically significant progressive keratoconus and visual loss in the study eye than those treated with standard care alone. The primary trial outcome finding was the demonstration that, on average at 18 months after randomization, patients receiving cross-linking in the study eye showed K2 that was 3 D lower than those receiving standard care, a statistically significant difference ($P = 0.002$). In addition, the 95% CI for the difference includes the clinically important difference of 1.5 D, which was the trial protocol definition of keratoconus progression. We found no adverse events associated with cross-linking, suggesting also that this is a relatively safe intervention. The secondary outcomes demonstrating that efficacy of cross-linking in halting keratoconus progression was clinically important were (1) a significant difference in uncorrected and best-corrected visual acuity ($P = 0.002$ and $P = 0.002$, respectively) between the trial arms and (2) the finding that only 2 patients (7%) randomized to cross-linking demonstrated keratoconus progression in the study eye compared with 12 patients (43%) in the standard care group at 18 months. Taken together, these findings provide clear evidence of the efficacy of cross-linking in stabilizing keratoconus progression in 10- to 16-year-olds.

These findings generally are in keeping with data from randomized controlled trials reported in a Cochrane review

Table 3. Keratometry in the Steepest Meridian in Study Eye at 18 Months after Randomization by Treatment Group

	Corneal Cross-linking		Standard Care			
	No.	*Mean (Standard Deviation)*	*No.*	*Mean (Standard Deviation)*	**Adjusted Difference (95% Confidence Interval)*,†**	**P Value**
Primary outcome						
K2 (D), ITT population	30	49.7 (3.8)	23	53.4 (5.8)	−3.00 (−4.93 to −1.08)	0.002
Sensitivity analysis of primary outcome						
K2 (D), PP population	28	49.4 (3.4)	19	53.2 (5.8)	−3.23 (−5.21 to −1.26)	0.001
K2 (D; including all scans with red flags)	30	49.7 (3.8)	25	54.5 (7.3)	−3.73 (−6.58 to −0.90)	0.01

D = diopter; ITT = intention-to-treat; K2 = keratometry in the steepest meridian; PP = per protocol.
*Adjusted difference is based on 58 patients in the ITT mixed model, 55 in the PP model, and 58 in the model including tomography scans with red flags who had a baseline K2 measurement and at least 1 follow-up examination.
†Adjusted for K2 and minimization factors site and number of eyes with progression at baseline.

Table 4. Secondary Outcomes at 18 Months by Treatment Group

	Corneal Cross-linking		Standard Care		Adjusted Difference, Unadjusted Odds Ratio, or Unadjusted Hazard Ratio (95% Confidence Interval)*	P Value
	No.	*Mean (Standard Deviation) or No. (%)*	*No.*	*Mean (Standard Deviation) or No. (%)*		
Apical corneal thickness (μm)	28	501.8 (38.0)	22	479.9 (46.3)	16.37 (−2.87 to 35.61)†	0.10
Uncorrected visual acuity (logMAR)‡	29	0.5 (0.3)	25	0.8 (0.6)	−0.31 (−0.50 to −0.11)†	0.002
Best-corrected visual acuity (logMAR)‡	29	0.4 (0.4)	25	0.6 (0.6)	−0.51 (−1.37 to 0.35)†	0.002
Refraction (spherical equivalent; D)	30	−0.6 (2.0)	25	−0.3 (2.3)	−0.75 (−1.69 to 0.18)†	0.25
Kmax (D)	30	57.0 (6.2)	22	60.3 (7.7)	−2.11 (−4.81 to 0.60)†	0.13
CVAQC score§	29	−1.2 (0.8)	25	−1.1 (0.9)	−0.26 (−0.69 to 0.14)†	0.22
CHU9D utility score‖	28	1.0 (0.1)	25	0.9 (0.1)	0.02 (−0.017 to 0.05)†	0.14
Confirmed keratoconus progression	30	2 (7%)	28	12 (43%)	0.10 (0.02 to 0.48)¶,#	0.004
Time to confirmed keratoconus progression	30	See Fig 4	30	See Fig 4	0.13 (0.03 to 0.59)¶,**	0.008

CHU9D = Child Health Utility 9D; CVAQC = Cardiff Visual Ability Questionnaire for Children; D = diopter; Kmax = maximum keratometry; logMAR = logarithm of the minimum angle of resolution.
*Adjusted for baseline and minimization factors site and number of eyes with progression at baseline.
†Adjusted difference.
‡Lower logMAR scores correspond to better visual acuity.
§Lower questionnaire scores indicate better outcome.[16]
‖Higher questionnaire scores indicate better outcome.
¶Analysis unadjusted because of the small proportion of participants having a progression event.
#Unadjusted odds ratio.
**Unadjusted hazard ratio.

comparing cross-linking with standard care for keratoconus in adult patients and reduce current uncertainty with regard to treatment. In the 3 trials eligible for inclusion in that review, the data suggest that eyes treated by cross-linking were less likely to show an increase in Kmax of 1.5 D or more at 12 months compared with eyes treated with standard care. On average, they reported that treated eyes had a less steep cornea (approximately 2 D less steep) and better uncorrected visual acuity (approximately 2 lines or 10 letters better; MD, −0.20 dB; 95% CI, −0.31 to −0.09 dB; n = 94 participants; n = 1 study; low-quality evidence).[7] The quality of the evidence was deemed low because it was derived largely from one trial at high risk of bias, the data on corneal thickness were inconsistent, and adverse effects were frequent but mostly transient. No randomized trial of cross-linking in young patients has been reported. Uncontrolled observational studies of cross-linking in keratoconus patients younger than 19 years have been published, each with limitations but each reporting effectiveness. Caporossi et al[12] reported an uncontrolled study of 152 keratoconus patients ranging in age from 10 to 18 years, for whom follow-up after cross-linking was available from only 61% of patients. In addition to short-term follow-up, the inclusion criteria included several parameters that are well recognized to be characterized by high intertest variability. In this treated patient group, a reduction in K2 of −0.4 D at 36 months was found, suggesting stabilization. Vinciguerra et al[13] reported 40 eyes treated with cross-linking from patients with progressive keratoconus who were 9 to 18 years of age (mean, 14.2 years of age) in a nonrandomized prospective study. Findings included reduced myopic spherical equivalent on refraction testing and reduction in mean K2 from 51.48 D before cross-linking to 50.21 D at 24 months. Our finding in the trial group treated with cross-linking of continued apical corneal thinning from baseline, although to a lesser extent than in the standard care group, is in keeping with other reports of results after cross-linking.[6,7]

We were unable to demonstrate a significant improvement in QoL between trial arms. Impact on QoL in keratoconus is influenced significantly by whether one or both eyes are affected,[27,28] for which reason a major determinant of QoL in the trial is very likely to have been the vision in the nonstudy eye. Moreover, the problems with reduced contact lens tolerance as keratoconus progresses and the eventual need to have corneal transplantation have major impacts on QoL and would not be expected in these trial participants with early keratoconus. Follow-up of KERALINK participants, including serial assessment of general and vision-related QoL outcomes, will continue to 4 years after randomization.

Because a high risk of progression of keratoconus to severe disease exists in children and young people, it is important to confirm the safety and efficacy of cross-linking in this population.[10] A strength of this trial is that the upper eligible age limit was 16 years, compared with previous uncontrolled studies in young patients that included patients up to the age of 19 years. Demonstration of efficacy in the younger patients is of additional importance because corneal tomography is becoming more widely available in community settings, which in turn will lead to younger age at diagnosis and referral to secondary care clinics. A further strength of our study is the use of a measurement protocol that addresses the key problem of measurement variability in corneal tomography, the standard imaging technique for assessing progression of keratoconus. Repeatability of most tomographic parameters is good in mild keratoconus but worsens as disease progresses, in particular the single steepest power measurement, Kmax.[20,26] To obtain data reliably identifying change, we used K2, the mean corneal power in the steepest corneal meridian, rather than Kmax as the

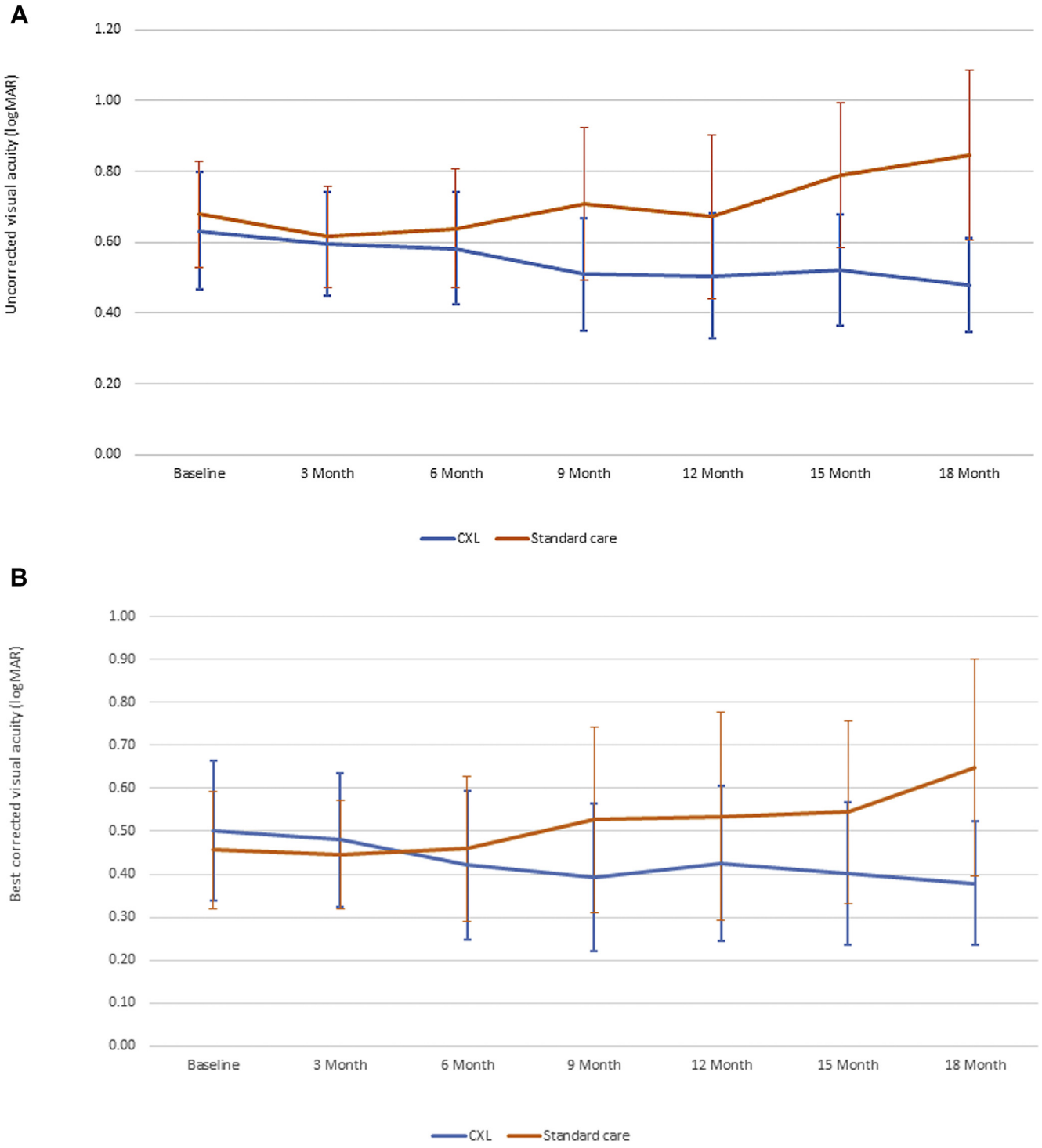

Figure 3. Line graphs showing (**A**) uncorrected visual acuity, (**B**), best-corrected visual acuity and (**C**) corneal thickness at the corneal apex in the study eye in the corneal cross-linking (CXL) and standard care groups at study visit intervals. Data are means. Error bars represent 95% confidence intervals of the mean. logMAR = logarithm of the minimum angle of resolution.

primary outcome measure. Because K2 is a measure of the mean curvature in the central 3-mm zone of the cornea, change in K2 would be expected to correlate with change in vision; Kmax is the maximum curvature or power, at whatever point that might be, and may not be close to the visual axis; thus, and as found in this trial, it can correlate poorly with vision effects of the ectasia. Because K2 represents a mean value, it inherently would allow more reliable discrimination between change of functional significance between study groups. Use of the mean of

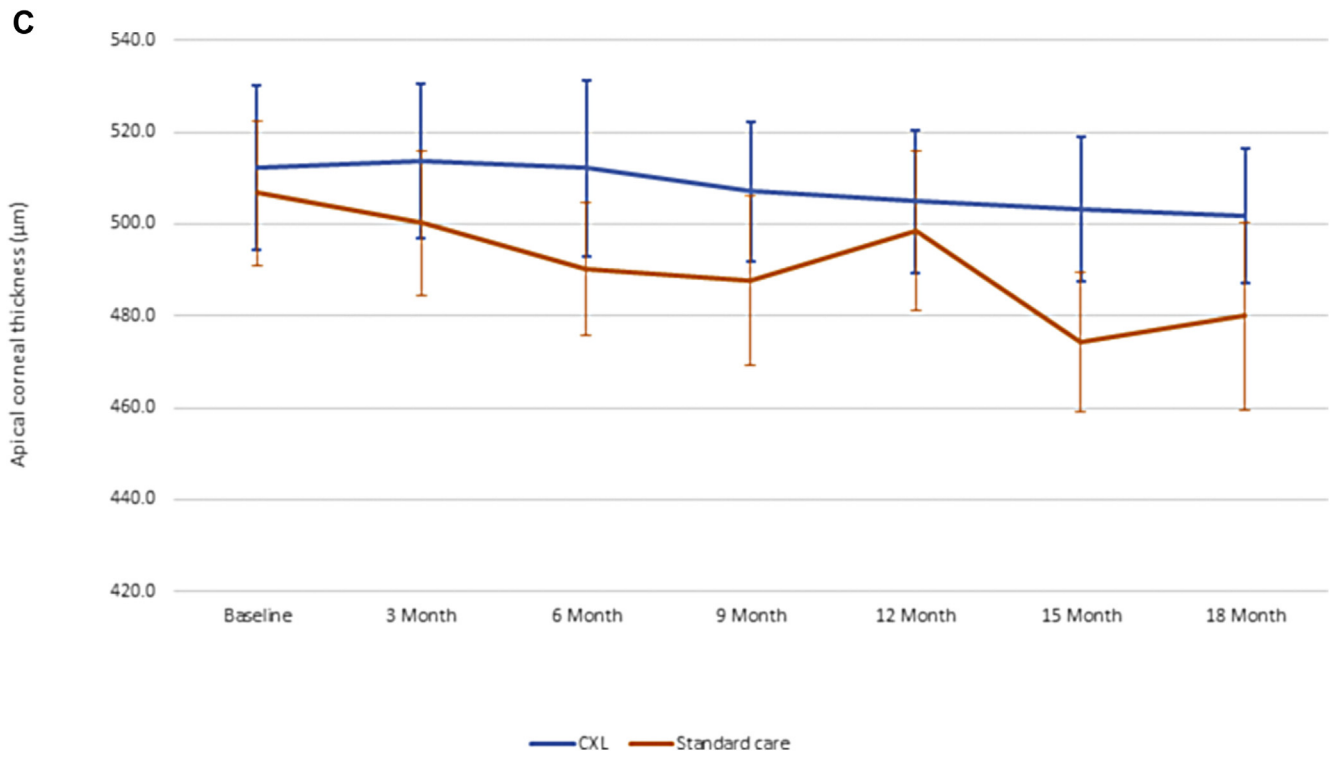

Figure 3. Continued

triplicate readings for all assessments—at trial eligibility screening, baseline, and outcome examinations—is a further methodologic strength that gives validity to the finding of differences in outcomes between the 2 trial groups. Finally, the definition of progression after randomization, a K2 increase of more than 1.5 D, corresponds to change in corneal power of visual significance.

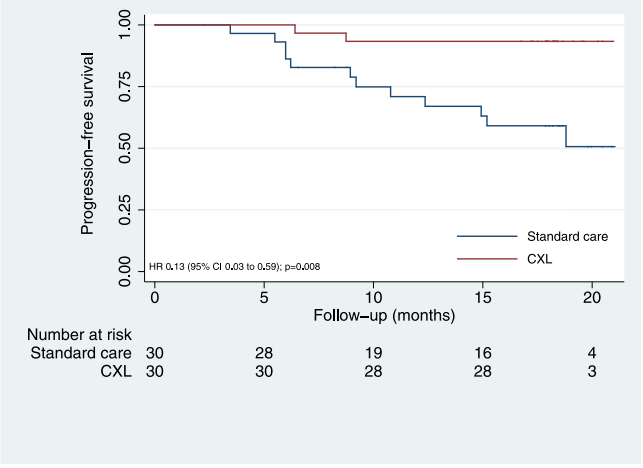

Figure 4. Kaplan-Meier plot showing time to keratoconus progression in corneal cross-linking (CXL) and standard care groups. Progression was defined as keratometry in the steepest meridian increase of more than 1.5 diopters with respect to value at randomization. CI = confidence interval; HR = hazard ratio.

Because known ethnic variation in prevalence of severe keratoconus exists, a limitation of our study may be the applicability of our findings to other populations. South Asian ethnicity is associated strongly with keratoconus in the United Kingdom[29,30] and accounted for 45% of patients recruited to this trial, a very significant overrepresentation compared with United Kingdom census statistics. However, this study is too small to demonstrate an interaction between treatment effect and ethnicity. An unanticipated measurement problem that emerged during the trial is that measurements of K2 in those eyes with most significant progression in some cases were marked with a red flag by Pentacam device software. In 2 patients in the standard care group at month 18, measurements from all 3 scans were excluded for this reason, although not specified in the trial protocol. However, sensitivity analyses of our primary outcome of K2, including all red flag measurements (Fig S1) and also a per-protocol analysis, did not change our conclusions.

Despite documented progression of 1.5 D before randomization, it is of interest that only 43% of patients receiving standard care subsequently showed progression clinically during the 18-month follow-up period. This suggests that the proportion of keratoconus patients who achieve spontaneous stabilization may be higher than expected, at least in 10- to 16-year-olds. Earlier reports from uncontrolled studies of effectiveness of cross-linking in halting keratoconus progression in

young patients now should be re-evaluated in the light of this observation. Although cross-linking is a relatively safe procedure, it is important that children with nonprogressive keratoconus are not managed by cross-linking.

The KERALINK study provides high-quality randomized evidence of efficacy of cross-linking in arresting progression of keratoconus in the great majority of young patients. Our data support a change in practice such that cross-linking should be considered for disease stabilization in young patients with evidence of keratoconus progression. In such patients with early-onset keratoconus in whom potential exists for further progression to the end of the third decade of life, particular benefit may be gained by avoiding the later requirement for contact lens wear or corneal transplantation. Evidence is emerging that cross-linking can reduce the risk of transplantation.[31,32]

Key questions to investigate are whether the arrest of keratoconus progression induced by cross-linking is permanent and whether an increasing proportion of those receiving standard care progress significantly. Longer follow-up of this trial population is already underway and will allow us to address these questions. A health economic evaluation modeling the impact of cross-linking in young patients, beyond the scope of our trial and taking into consideration KERALINK longer-term follow-up data, is warranted. The first cost-effectiveness analyses based on adult cross-linking studies reported a high likelihood of cost effectiveness.[33,34] Cross-linking is an efficacious and safe intervention that stabilizes keratoconus progression in young patients; in the event that stabilization is sustained, our findings may be the first line of evidence justifying the screening of young patients with astigmatism for keratoconus and consideration of early cross-linking before significant visual loss has occurred.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the UK Health Research Authority, the Medicines and Healthcare Products Regulatory Agency, and Brent Ethics Committee approved the study. All research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from parents of all recruited participants.

No animal subjects were included in this study.

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Obtained funding: Larkin, with input from Burr, Bunce, and Doré

Overall responsibility: Larkin, Chowdhury, Burr, Raynor, Edwards, Tuft, Bunce, Caverly, Doré

Abbreviations and Acronyms:
CI = confidence interval; **D** = diopter; **Kmax** = maximum keratometry in the steepest meridian; **K2** = keratometry in the steepest meridian; **QoL** = quality of life; **SD** = standard deviation.

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